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EXAMINER	
WOODWARD, CHERIE MICHELLE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/804,845	HARRIS ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *17-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's facsimile of 28 June 2006 amending the numbering of claims to administratively correct the typographical error of two (2) claims numbered "13" is acknowledged.

Election/Restrictions

2. Applicant's election without traverse of Group I (claims 1-16) in the reply filed on 16 May 2006 is acknowledged. Claims 1-34 are pending. Claims 17-34 are withdrawn as being drawn to non-elected inventions. Claims 1-16 are under examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 10 January 2006 has been considered insofar as possible. A signed copy is attached hereto. Entries that are lined through have not been considered for the following reasons: 37 CFR 1.98(a)(2) requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Additionally, 37 CFR 1.98(a)(1) requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement.

The PCT International Search Report dated 8/11/2005 has not been considered. Each individual reference listed in the Report should be submitted for consideration, to the extent that they have not already been considered and/or cited by the examiner. The references will be considered upon receipt of the documents. The "Diamyd" document dated 5/2/2002 (item 9) has not been considered because a certified English translation was not provided. The document will be considered upon the receipt of a certified English translation. Documents with recited hyperlinks have been considered to the extent that they were furnished by Applicant or otherwise available online.

The PCT International Bureau documents and WO document have not been considered because they could not be located by the information provided on the form 1449 and no copy was provided. They

will be considered upon receipt. 37 CFR 1.98(a)(2) requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed.

Specification - Objections

4. The use of the trademarks SUSTACAL (pp.18 and 19), ALHYDROGEL (pp. 13-14), ALHYDROGEL-DIAMYD (p. 25), and DIAMYD (pp. 27, 28, 33-34) have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The disclosure is objected to because of the following informalities: there are blank spaces on page 1 of the disclosure. There is also an obscure square symbol on page 22, last line. Appropriate correction is required. Applicant is reminded that no new matter should be added.

Provisional Obviousness-Type Double Patenting Rejection

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or

claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-11 of copending Application No. 10/842,715. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to the same methods, each rendering the other obvious: a method of suppressing an immune response in a human by administering to a human an effective immunosuppressive does of GAD65, wherein the administration is subcutaneous, wherein the adjuvant is aluminum hydroxide, wherein the dose range is about 10 to about 50 micrograms.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite administration for "an effective time." The metes and bounds of the phrase are not limited and cannot be discerned from the disclosure.

10. Claims 1, 4, 6, 8, 11, and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the phrase "at a level of at least 20 micrograms." The upper limit of the range is not define or limited. Additionally, it is unclear from the claims, as written, whether the "level" referred to is the level of human recombinant GAD65 protein to be administered in the booster dose or whether the "level" refers to the total combined doses (first administration and booster dose). Is the "level" to be measured so that the "level of at least 20 micrograms" can be determined? If so, the claims are missing a measurement determination and correlation step.

11. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the measurement and correlation step. In order to determine the level of insulin production existing prior to administration of an effective amount of human recombinant GAD65 protein, a measurement of insulin must be taken. The claims, as written, fail to recite a measurement step. Additionally, if the administration of the recombinant human GAD65 protein is stimulate production of insulin above the level existing prior to administration of the protein, a correlation step should be included.

12. Claim 11 recites the limitation "said at least one adjuvant" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 11 is dependent from claim 8. However, claim 8 does not encompass the limitation of having "at least one adjuvant."

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Lernmark et al., Abstract 32-LB, Presented at the ADA meeting, June 2003 (www.diamyd.com/docs/PressDocs.aspx?PageID=11&sm=bc).

The claims recite a method of treating diabetes in a human comprising administering an effective amount of a human recombinant GAD65 protein and at least one adjuvant for an effective time so as to stimulate the production of insulin in said human to a level above that existing prior to said administration; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the

booster is administered in a dosage such that the human recombinant protein is at a level of at least 20 microgram; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is in the range of from about 20 micrograms to about 500 micrograms; a method for suppressing or reducing the immune response of a human to glutamic acid decarboxylase comprising administering to said human an effective immunosuppressive dose of human recombinant GAD65 protein; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; wherein the level of β-cell function is determined through measurement of CD4+ lymphocytes prior to said at least one booster dosage.

Lernmark et al., teach administration of a alum-formulated GAD65 vaccine (DIAMYD™) to non-insulin requiring diabetes patients using prime and boost dose regimes, formulated in 4μg, 20μg, 100μg, and 500μg subcutaneous injections, designed to induce immunological tolerance (abstract, first column, first paragraph). Figure 3 shows peripheral blood lymphocytes, including total T-cells, at day 1, weeks 1, 4, 6, and 24 for dose levels of 4μg, 20μg, 100μg, and 500μg of the alum-formulated GAD65 vaccine, DIAMYD™.

15. Claims 1-13 and 15 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kaufman et al., US Patent 6,022,697 (8 February 2000, priority to 29 November 1996).

The claims recite a method of treating diabetes in a human comprising administering an effective amount of a human recombinant GAD65 protein and at least one adjuvant for an effective time so as to stimulate the production of insulin in said human to a level above that existing prior to said administration; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage

such that the human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is at a level of at least 20 microgram; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is in the range of from about 20 micrograms to about 500 micrograms; a method for suppressing or reducing the immune response of a human to glutamic acid decarboxylase comprising administering to said human an effective immunosuppressive dose of human recombinant GAD65 protein; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; wherein the level of β-cell function is determined through measurement of CD4+ lymphocytes prior to said at least one booster dosage.

Kaufman et al., ('697 patent) teach methods for diagnosis and treatment of insulin-dependent diabetes mellitus by administering to a mammal a therapeutically effective amount of a β-cell-associated autoantigen (column 4, lines 28-31) such as the recombinant human GAD65 protein (column 2, lines 56-67 to column 3, lines 1-5; column 8, lines 14-15 (incorporating by reference the recombinant human GAD65 protein from US Patent 5,475,086)) subcutaneously (column 9, lines 12-15) in a therapeutically effective amount (column 9, lines 51-62), including one or more dose administrations or boosted in regular intervals (column 9, lines 62-63) wherein the administration of the antigen results in an increase in the ration of the number of Th2 cells specific for that antigen to the number of Th1 cells specific for that antigen. The antigen may be administered alone or in combination with an adjuvant for the purpose of increasing the Th2/Th1 ratio (column 4, lines 32-38). Adjuvants, including aluminum hydroxide are

taught at column 10, lines 1-19, especially lines 10-11. Injections of 50 µl GAD65 are taught at column 11, line 33. Residual islet cell function following GAD65 administration is taught at column 15, lines 27.

16. Claims 1-13 and 15 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Diamyd Medical, Press release, Quarterly Report II – 99/00, Stockholm, 3 May 2000 (www.diamyd.com/docs/PressClip.axpx?PageID=10&LangID=2&ClipID-135&sm=b_b)

The claims recite a method of treating diabetes in a human comprising administering an effective amount of a human recombinant GAD65 protein and at least one adjuvant for an effective time so as to stimulate the production of insulin in said human to a level above that existing prior to said administration; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is at a level of at least 20 microgram; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is in the range of from about 20 micrograms to about 500 micrograms; a method for suppressing or reducing the immune response of a human to glutamic acid decarboxylase comprising administering to said human an effective immunosuppressive dose of human recombinant GAD65 protein; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms.

The Diamyd Medical press release entitled "Quarterly Report II – 99/00", published on 3 May 2000, recites an alum-based GAD65 diabetes vaccine (page 1 of 5, paragraph identified as "1. Efficacy

Study"). Vaccine doses of 20 to 500 micrograms of DIAMYD™ (identified as the diabetes vaccine at p. 1of 5, paragraph 3) were administered subcutaneously in separate and ascending dose levels to human volunteers (p. 3 of 5, paragraph identified as "17. Clinical Phase I with Humans").

17. Claims 1-2, 4-9, 11-16 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Tobin et al., US Patent 5,846,740 (8 December 1998, priority to 21 September 1990).

The claims recite a method of treating diabetes in a human comprising administering an effective amount of a human recombinant GAD65 protein and at least one adjuvant for an effective time so as to stimulate the production of insulin in said human to a level above that existing prior to said administration; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is at a level of at least 20 microgram; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is in the range of from about 20 micrograms to about 500 micrograms; a method for suppressing or reducing the immune response of a human to glutamic acid decarboxylase comprising administering to said human an effective immunosuppressive dose of human recombinant GAD65 protein; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; wherein the level of β-cell function is determined through measurement of CD4+ lymphocytes prior to said at least one booster dosage.

Tobin et al., ('740 patent) teach a method for therapeutically treating patients, including people (column 1, line 23) having or at risk for having an autoimmune response associated with GAD65 (column 9, lines 38-40) to induce immunotolerance (column 9, line 42) using recombinant GAD65 polypeptides (column 2, lines 20-28). Variable dosages that can be optimized with routine experimentation are taught at column 14, lines 48-55. Subcutaneous administration is taught at column 14, line 61. Preservatives and other additives are taught at column 15, lines 5-10. Inclusion of adjuvants in the immunization protocol are taught at column 7, lines 15-16. Preparations of medicaments or pharmaceutical compositions are taught at column 15, lines 11-15. Dosage of 10μg/ml of antigen (7μM peptide) is taught at column 26, line 58. Human GAD65 is taught at column 32, line 43. Administration of 25μg GAD65 in an adjuvant is taught at column 42, lines 2-4. Characterization of GAD-reactive Tcells, including CD4+ cells are taught in Example 7 (column 30, line 42 to column 32, line 8). Peptide-based immunotherapeutic agents useful in predicting and ameliorating human IDDM are taught at column 33, lines 45-51.

18. Claims 1-2, 4-9, 11-13, and 15 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Baekkeskov et al., US Patent 5,998,584 (7 December 1999, priority to 17 October 1997).

The claims recite a method of treating diabetes in a human comprising administering an effective amount of a human recombinant GAD65 protein and at least one adjuvant for an effective time so as to stimulate the production of insulin in said human to a level above that existing prior to said administration; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is at a level of at least 20 microgram; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is in the range of from about 20 micrograms to about 500 micrograms; a method for suppressing or reducing the immune response of a human to glutamic acid decarboxylase comprising administering to said human an effective immunosuppressive dose of human recombinant GAD65 protein; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65

protein and at least one adjuvant are administered in a dosage such that the GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms.

Baekkeskov et al., ('584 patent) teach methods for the diagnosis and treatment of diabetes using recombinant GAD65 (column 4, lines 56-67; column 8, lines 31-48). Induction of immunotolerence by administration of GAD65 is taught at column 17, lines 17-65. Intradermal administration of GAD65 in the presence of adjuvants is taught at column 17, lines 32-33 and column 19, line 67 to column 20, line 1. . GAD65 soluble fragments incorporated into pharmaceutical compositions useful to attenuate, inhibit or prevent the destruction of pancreatic β-cells associated with the onset of insulin-dependent diabetes are taught at column 18, lines 64-67 to column 19, line 1. Pharmaceutically acceptable adjuvants are taught at column 19, line 9. The concentration of GAD65 peptide in the pharmaceutical composition is taught at column 19, lines 11-15, and includes dose ranges of 1 to 100μg of purified ligand (column 19, lines 58-59). Recombinant baculovirus vectors expressing human GAD65 are taught at column 20, lines 38-52.

19. Claims 1-2, 4-9, and 11-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Harrison et al., WO 96/26218 (international publication date 29 August 1996).

The claims recite a method of treating diabetes in a human comprising administering an effective amount of a human recombinant GAD65 protein and at least one adjuvant for an effective time so as to stimulate the production of insulin in said human to a level above that existing prior to said administration; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is at a level of at least 20 microgram; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the

booster is administered in a dosage such that the human recombinant protein is in the range of from about 20 micrograms to about 500 micrograms; a method for suppressing or reducing the immune response of a human to glutamic acid decarboxylase comprising administering to said human an effective immunosuppressive dose of human recombinant GAD65 protein; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; wherein the level of β-cell function is determined through measurement of CD4+ lymphocytes prior to said at least one booster dosage.

WO 96/26218 teaches a method of therapeutic treatment of diabetes by inducing immunological tolerance to eliminate or diminish reactivity of autoreactive T-cells or antibodies to IDDM autoantigens using peptides or peptide derivatives of human recombinant GAD65 (page 6, lines 28-32 to page 7, line 2; page 1, line 25; Figure 1). Dosage of peptide range from 0.1μg to 10mg per dose and preferably 1.0μg to 1 mg per dose, including one or multiple doses (page 8, lines 29-32). Subcutaneous administration is taught at page 9, line 1. Administration alone or with an adjuvant is taught at page 9, lines 3-6. Human GAD65 is taught at page 9, line 30. T-cell proliferative responses to administration of GAD65 are taught at p. 15, Example 4 and Table 2, page 20.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et al., WO 96/26218 (international publication date 29 August 1996) in view of Kaufman et al., US Patent 6,022,697 (8 February 2000, priority to 29 November 1996), *supra*.

The claims recite a method of treating diabetes in a human comprising administering an effective amount of a human recombinant GAD65 protein and at least one adjuvant for an effective time so as to stimulate the production of insulin in said human to a level above that existing prior to said administration; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is at a level of at least 20 microgram; additionally comprising administering at least one booster dose of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein wherein the booster is administered in a dosage such that the human recombinant protein is in the range of from about 20 micrograms to about 500 micrograms; a method for suppressing or reducing the immune response of a human to glutamic acid decarboxylase comprising administering to said human an effective

immunosuppressive dose of human recombinant GAD65 protein; wherein the administration is subcutaneous; wherein the adjuvant is aluminum hydroxide; wherein the human recombinant GAD65 protein and at least one adjuvant are administered in a dosage such that the GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is at a level of at least 20 micrograms; additionally comprising administering at least one booster dosage of human recombinant GAD65 protein following the first administration of human recombinant GAD65 protein and wherein said booster is administered in a dosage such that said human recombinant GAD65 protein is in the range of from about 20 micrograms to about 500 micrograms; wherein the level of β-cell function is determined through measurement of CD4+ lymphocytes prior to said at least one booster dosage.

WO 96/26218 teaches a method of therapeutic treatment of diabetes by inducing immunological tolerance to eliminate or diminish reactivity of autoreactive T-cells or antibodies to IDDM autoantigens using peptides or peptide derivatives of human recombinant GAD65 (page 6, lines 28-32 to page 7, line 2; page 1, line 25; Figure 1). Dosage of peptide range from 0.1μg to 10mg per dose and preferably 1.0μg to 1 mg per dose, including one or multiple doses (page 8, lines 29-32). Subcutaneous administration is taught at page 9, line 1. Administration alone or with an adjuvant is taught at page 9, lines 3-6. Human GAD65 is taught at page 9, line 30. T-cell proliferative responses to administration of GAD65 are taught at p. 15, Example 4 and Table 2, page 20. Although aluminum hydroxide is a well-known adjuvant, WO 96/26218 does not teach aluminum hydroxide.

Kaufman et al., ('697 patent) teach methods for diagnosis and treatment of insulin-dependent diabetes mellitus by administering to a mammal a therapeutically effective amount of a β-cell-associated autoantigen (column 4, lines 28-31) such as the GAD65 protein (column 2, lines 56-67 to column 3, lines 1-5) subcutaneously (column 9, lines 12-15) in a therapeutically effective amount (column 9, lines 51-62), including one or more dose administrations or boosted in regular intervals (column 9, lines 62-63). Adjuvants, including aluminum hydroxide are taught at column 10, lines 1-19, especially lines 10-11. Injections of 50 μl GAD65 are taught at column 11, line 33.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of WO 96/26218 with the well-known adjuvant, aluminum hydroxide, to effect a method for suppressing or reducing the immune response of a human by administering an immunosuppressive dose of recombinant GAD65 protein in an adjuvant of aluminum

hydroxide. The person of ordinary skill in the art would have been motivated to make the modification to select aluminum hydroxide because WO 96/26218 teaches that a pharmaceutical composition of human GAD65 in any adjuvant is acceptable and would produce an immunosuppressive effect against autoreactive T-cells in a dose range of from 0.1μg to 10mg per dose of peptide and preferably 1.0μg to 1 mg per dose of peptide. One of ordinary skill reasonably would have expected success because aluminum hydroxide has been used as an adjuvant since 1934 (see, for exemplary purposes only, Fiejka et al., Rocz Ranstw Zakl Hig. 1993; 44(1):73-80, Abstract Only; HogenEsch H., Vaccine 2002 may 31; 20 Suppl 3:S34-9, Abstract Only; Hem et al., Pharm Biotechnol 1995; 6:249-76, Abstract Only; Redhead et al., Pharmacol Toxicol. 1992 Apr; 70(4):278-80, Abstract Only). Additionally, Kaufman et al., successfully teach administration of recombinant human GAD65 in an adjuvant of aluminum hydroxide.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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